IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

PUBLIC PATENT FOUNDATION, INC., a New York, not-for-profit corporation, Plaintiff, v. NOVARTIS CONSUMER HEALTH, INC., a Delaware corporation, Defendant.	Civil Action No. 1:10-cv-01268 Honorable William J. Hibbler **JURY TRIAL DEMANDED**

SECOND AMENDED COMPLAINT FOR FALSE PATENT MARKING

Plaintiff, PUBLIC PATENT FOUNDATION, INC. ("Relator" or "Plaintiff"), by its attorneys, hereby complains against Defendant, NOVARTIS CONSUMER HEALTH, INC. ("Defendant"), as follows:

I.

NATURE OF THE CASE

1. This is a *qui tam* action on behalf of the public for false patent marking under 35 U.S.C. §292.

2. As set forth below, Defendant has violated 35 U.S.C. §292(a), by marking its Prevacid®24HR branded product with United States Patent Number 4,628,098 ("the '098 Patent") even though the '098 Patent expired no later than May 10, 2009.

3. Prevacid®24HR is an over-the-counter treatment for frequent heartburn.

4. This case presents an exceptionally egregious example of false patent marking, causing harm to consumers. Defendant has brazenly marked, and continues to mark, packaging, packaging inserts and advertisements for Prevacid®24HR with the '098 Patent, even though there was never a single moment in time when Defendant's Prevacid®24HR branded product

was actually protected by the '098 patent. Instead, Defendant first launched its Prevacid®24HR product on November 12, 2009 (*see* Press Release dated November 12, 2009, attached hereto as Exhibit A), about six (6) months **after** the '098 patent expired. This was no coincidence. Prevacid®24HR is the brand name of a non-prescription treatment product that owes its very existence to the **absence** of patent protection.

5. Defendant was apparently motivated to pursue an aggressive strategy of false patent marking because it knew that it would have to compete for market share with other makers of non-prescription medicine, in particular, other makers of non-prescription heartburn treatments. To both establish, and then improperly preserve, its first to market advantage in both pricing and market share, Defendant wanted to create the false impression in the minds of consumers that its Prevacid®24HR product is somehow unique and "worthy" of patent protection.

6. Defendant's strategy of false patent marking has caused significant harm to consumers as they are being directly misled into believing that the Prevacid®24HR product is covered by present and prospective patent rights, when that representation is patently false.

7. Upon information and belief, Defendant marks its Prevacid®24HR branded product with the expired '098 Patent with the intent to deceive the public and to gain a competitive advantage in the market.

8. The expiration date of a U.S. Patent is not readily ascertainable by members of the public at the time of product purchase. The patent number itself does not provide members of the public with the expiration date of the patent. Basic information about a patent, such as the filing, issue and priority dates associated with a particular U.S. patent number are available at, for example, the website of the United States Patent and Trademark Office, ("USPTO"). However, access to the Internet is necessary to retrieve that information (meaning that a

consumer may not have the ability to retrieve the information while he is in a store making a purchasing decision) and even after retrieving that information, it does not include the expiration date of a patent. Rather, a member of the public must also conduct a burdensome legal analysis, requiring specific knowledge of U.S. patent laws regarding patent term expiration.[1] Notably, a correct calculation of the expiration date must also account for at least: a) any term extensions granted by the USPTO, which may or may not be present on the face of the patent, and b) whether or not the Patent owner has paid the necessary maintenance fees.

9. Defendant is a subsidiary of pharmaceutical giant Novartis AG, headquartered in Basel, Switzerland.

10. Upon information and belief, Defendant's false marking in this case was no oversight, was not caused by mistake and was not an isolated incident. Instead, it is part of an apparently deliberate false marking strategy pursued by Defendant and other subsidiaries of Novartis AG, which have systematically engaged in false marking practices for the purpose of deceiving the public. There are currently at least five other false marking cases pending against subsidiaries of Novartis AG.[2]

11. Plaintiff seeks an award of monetary damages against Defendant pursuant to 35 U.S.C. §292(b) of up to $500 for each offense, with one-half going to the use of the United States and the other half going to the person bringing the action.

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[1] Pursuant to 35 U.S.C. §154 (a)(2) and (c), the term of a patent, provided that all required maintenance fees are paid, are: i) for applications filed on or after June 8, 1995, the patent term is 20 years from the filing date of the earliest U.S. application to which priority is claimed, ii) for applications that were pending on and for patents that were still in force on June 8, 1995, the patent term is either 17 years for the issue date or 20 years from the filing date of the earliest U.S. application to which priority is claimed, whichever is longer. *See also*: Manual of Patent Examining Procedure ("MPEP") §2701, available at http://www.uspto.gov/web/offices/pac/mpep/ documents/ 2700_2701.htm.

[2] Currently pending are the following false marking cases: 1) *Harrington v. CIBA Vision Corp.* (3:08-cv-00251, NCWD 2008) for the product AOSEPT®, 2) *Simonian v. CIBA Vision Corp.* (1:10-cv-01202, ILND 2010) for the product CLEAR CARE®, 3) *Simonian v. Novartis Animal Health US, Inc.* (1:10-cv-01267, ILND 2010) for the product INTERCEPTOR®, 4) *Simonian v. Novartis Pharmaceuticals Corp.* (1:10-cv-01308, ILND 2010) for the product HYPO-TEARS®, and 5) *Baker v. Novartis Pharmaceuticals Corp, et al.* (2:10-cv-02272, TNWD 2010) for the products DENAGARD®, MILBEMITE® and OCUPRESS®.

II.

THE PARTIES

12. Relator, the Public Patent Foundation, Inc. is a New York, not-for-profit corporation, with a principal place of business located at Benjamin N. Cardozo School of Law, 55 Fifth Avenue, New York, New York 10003.

13. Defendant NOVARTIS CONSUMER HEALTH, INC. is a Corporation established under the laws of the State of Delaware with its principal place of business at 200 Kimball Drive, Parsippany, New Jersey 07054-0622.

14. Defendant is one of the largest pharmaceutical companies in the world.

15. The prescription version of Defendant's Prevacid®24HR product was made and marketed by Takeda Pharmaceutical under the brand Prevacid®.

16. The prescription medicine Prevacid® (lansoprazole) was one of the top five prescription brands in the United States achieving $3.37 billion in annual sales in 2008 (*see* Press Release dated May 14, 2009, attached hereto as Exhibit B).

17. Defendant "has licensed the Prevacid® trademark and certain other intellectual property rights for the over-the-counter development and commercialization from Takeda Pharmaceuticals North America, Inc." (*see* Exhibit B).

18. Defendant and Takeda Pharmaceuticals partnered in making the prescription medicine Prevacid® available as an over-the-counter treatment for frequent heartburn (*see* Exhibit B).

19. On or about May 14, 2009, the U.S. Food and Drug Administration (FDA) approved Defendant's Prevacid®24HR (lansoprazole delayed-release capsules 15 mg) "as the

first over-the-counter (OTC) Proton Pump Inhibitor (PPI) for the treatment of frequent heartburn since 2003." (*see* Exhibit B).

20. Defendant first launched its Prevacid®24HR product on November 12, 2009, making it "available in more than 100,000 pharmacies, drug stores, supermarkets, mass merchandisers and other retail locations throughout the US." (*see* Exhibit A).

21. Upon information and belief, Defendant has marked at least the product packaging, and the package insert of its Prevacid®24HR product with the '098 Patent since at least November 12, 2009.

22. The official product launch of Prevacid®24HR on November 12, 2009, occurred about six (6) months **after** the '098 patent expired.

III.

JURISDICTION AND VENUE

23. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

24. Venue properly lies in the Northern District of Illinois pursuant to 28 U.S.C. §§ 1391(c), and 1395(a), because Defendant's falsely marked products were and are offered for sale and sold in this District.

25. This Court has personal jurisdiction over Defendant because it has sold and continues to sell its falsely marked products, in Illinois and in this District and/or in the stream of commerce with knowledge that they would be sold in Illinois and in this District. Upon information and belief, such sales by Defendant are substantial, continuous, and systematic.

IV.

COUNT I – FALSE MARKING OF THE '098 PATENT

26. Plaintiff incorporates paragraphs 1-25 as if fully set forth herein.

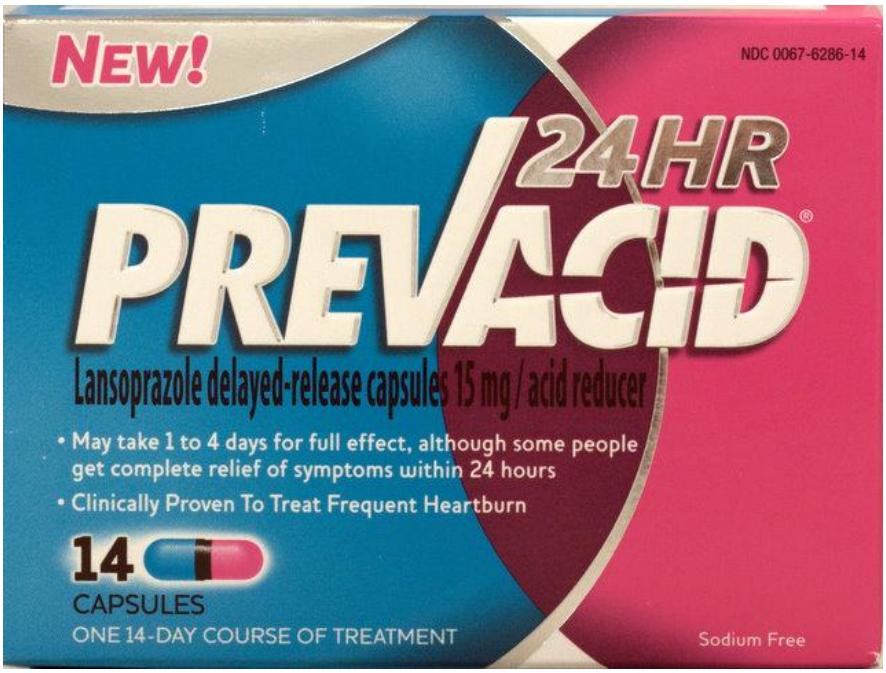
27. The ‘098 Patent, entitled “2-[2-pyridylmethylthio-(sulfinyl)]benzimidazoles,” was filed on July 29, 1985, issued on December 9, 1986 and was originally set to expire on July 29, 2005. On January 6, 1997, the USPTO granted the ‘098 Patent a term extension of 1,381 days pursuant to 35 U.S.C. § 156, extending the expiration date of the ‘098 Patent to May 10, 2009. Upon information and belief, the owner of record of the ‘098 Patent is Takeda Pharmaceutical. A true and correct copy of the ‘098 Patent including the Certificate Extending Patent Term is attached hereto as Exhibit C.

28. Defendant has in the past manufactured and marketed, or caused to be manufactured and marketed, and presently manufactures and markets, or causes to be manufactured or marketed, products for sale to the general consuming public, including, for example, its Prevacid®24HR branded drug for treating heartburn.

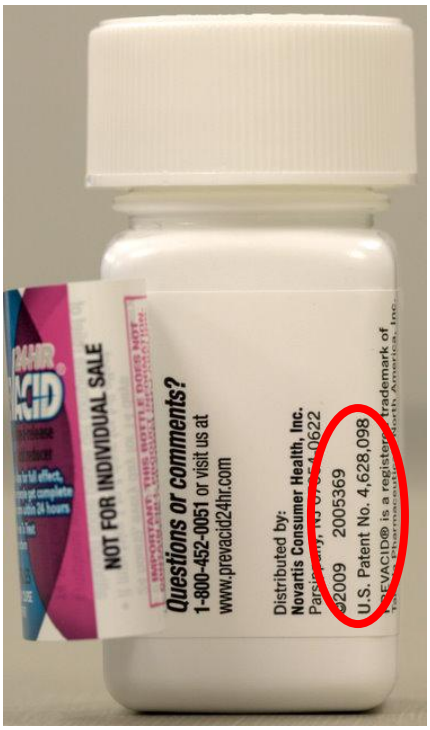
29. The ‘098 Patent expired no later than May 10, 2009.

30. Upon information and belief, Defendant has in the past marked, or caused to be marked, and presently marks, or causes to be marked, for example, but not limited to, at least the following products and/or packaging thereof, with the expired ‘098 patent: Prevacid®24HR.

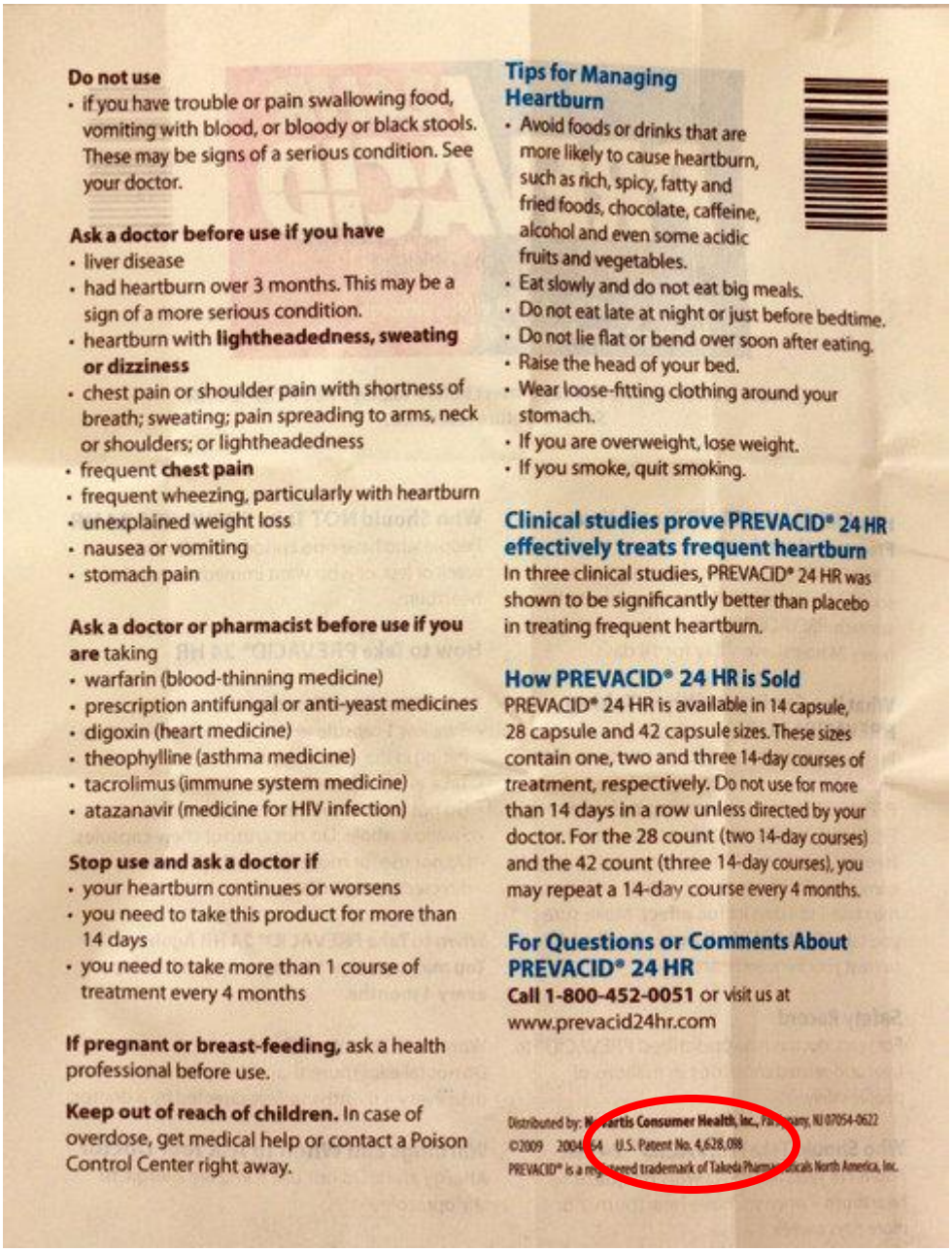
31. Prevacid®24HR is currently sold in packaging marked as shown below (emphasis added):


NEW!
NDC 0067-6286-14
24HR
PREVACID®
Lansoprazole delayed-release capsules 15 mg / acid reducer
• May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours
• Clinically Proven To Treat Frequent Heartburn
14
CAPSULES
ONE 14-DAY COURSE OF TREATMENT
Sodium Free


LOT: 09594
EXP: 04/2011
MADE IN: ITALY
KEEP THE CARTON AND PACKAGE INSERT. THEY CONTAIN IMPORTANT INFORMATION.
TAMPER-EVIDENT BOTTLE.
DO NOT USE IF INNER FOIL SEAL IMPRINTED WITH "SEALED for YOUR PROTECTION" OR BLACK BAND AROUND THE CENTER OF EACH CAPSULE IS MISSING OR BROKEN.
NOVARTIS
Distributed by:
U.S. Patent No. 4,628,098



32. The "Package Insert" referred to on the Prevacid®24HR packaging includes a marking of the expired '098 patent. An exemplary "Package Insert" is shown below (emphasis added)(next page):



Do not use
- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.

Ask a doctor before use if you have
- liver disease
- had heartburn over 3 months. This may be a sign of a more serious condition.
- heartburn with **lightheadedness, sweating or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are taking
- warfarin (blood-thinning medicine)
- prescription antifungal or anti-yeast medicines
- digoxin (heart medicine)
- theophylline (asthma medicine)
- tacrolimus (immune system medicine)
- atazanavir (medicine for HIV infection)

Stop use and ask a doctor if
- your heartburn continues or worsens
- you need to take this product for more than 14 days
- you need to take more than 1 course of treatment every 4 months

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Tips for Managing Heartburn
- Avoid foods or drinks that are more likely to cause heartburn, such as rich, spicy, fatty and fried foods, chocolate, caffeine, alcohol and even some acidic fruits and vegetables.
- Eat slowly and do not eat big meals.
- Do not eat late at night or just before bedtime.
- Do not lie flat or bend over soon after eating.
- Raise the head of your bed.
- Wear loose-fitting clothing around your stomach.
- If you are overweight, lose weight.
- If you smoke, quit smoking.

Clinical studies prove PREVACID® 24 HR effectively treats frequent heartburn
In three clinical studies, PREVACID® 24 HR was shown to be significantly better than placebo in treating frequent heartburn.

How PREVACID® 24 HR is Sold
PREVACID® 24 HR is available in 14 capsule, 28 capsule and 42 capsule sizes. These sizes contain one, two and three 14-day courses of treatment, respectively. Do not use for more than 14 days in a row unless directed by your doctor. For the 28 count (two 14-day courses) and the 42 count (three 14-day courses), you may repeat a 14-day course every 4 months.

For Questions or Comments About PREVACID® 24 HR
Call 1-800-452-0051 or visit us at www.prevacid24hr.com

Distributed by: **Novartis Consumer Health, Inc.,** Parsippany, NJ 07054-0622
©2009 2004864 U.S. Patent No. 4,628,098
PREVACID® is a registered trademark of Takeda Pharmaceuticals North America, Inc.

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©2009 2004864 U.S. Patent No. 4,628,098
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33. Defendant currently markets Prevacid®24HR with a marking of the expired '098 patent on its website (*see* http://www.prevacid24hr.com/pdfs/PackageInsert.pdf, last viewed April 27, 2010), as shown below (emphasis added):

Please read the entire package insert before taking PREVACID® 24 HR. Save for future reference.

How PREVACID® 24 HR Treats Your Frequent Heartburn

PREVACID® 24 HR stops acid production at the source – the **pumps** that release acid into the stomach. PREVACID® 24 HR is taken once a day (every 24 hours), every day for 14 days.

What You Can Expect When Taking PREVACID® 24 HR

Frequent heartburn can occur anytime during the 24-hour period (day or night). Take PREVACID® 24 HR in the morning before eating. PREVACID® 24 HR is clinically proven to treat frequent heartburn. Although some people get complete relief of symptoms within 24 hours, it may take 1 to 4 days for full effect. Make sure you take PREVACID® 24 HR every day for 14 days to treat your frequent heartburn.

Safety Record

For years, doctors have prescribed PREVACID® to treat acid-related conditions in millions of people safely.

Who Should Take PREVACID® 24 HR

Adults (18 years and older) with **frequent heartburn** – when you have heartburn 2 or more days a week.

Who Should NOT Take PREVACID® 24 HR

People who have one episode of heartburn a week or less, or who want immediate relief of heartburn.

How to Take PREVACID® 24 HR

14-DAY Course of Treatment

- Swallow 1 capsule with a glass of water before eating in the morning.
- Take every day for 14 days.
- Do not take more than 1 capsule a day.
- Swallow whole. Do not crush or chew capsules.
- Do not use for more than 14 days unless directed by your doctor.

When to Take PREVACID® 24 HR Again

You may repeat a 14-day course of therapy every 4 months.

When to Talk to Your Doctor

Do not take for more than 14 days or more often than every 4 months unless directed by a doctor.

Warnings and When to Ask Your Doctor

Allergy alert: Do not use if you are allergic to lansoprazole

Do not use

- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.

Ask a doctor before use if you have
- liver disease
- had heartburn over 3 months. This may be a sign of a more serious condition.
- heartburn with **lightheadedness, sweating or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are taking
- warfarin (blood-thinning medicine)
- prescription antifungal or anti-yeast medicines
- digoxin (heart medicine)
- theophylline (asthma medicine)
- tacrolimus (immune system medicine)
- atazanavir (medicine for HIV infection)

Stop use and ask a doctor if
- your heartburn continues or worsens
- you need to take this product for more than 14 days
- you need to take more than 1 course of treatment every 4 months

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

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- Avoid foods or drinks that are more likely to cause heartburn, such as rich, spicy, fatty and fried foods, chocolate, caffeine, alcohol and even some acidic fruits and vegetables.
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For Questions or Comments About PREVACID® 24 HR
Call 1-800-452-0051 or visit us at www.prevacid24hr.com

Distributed by: Novartis Consumer Health, Inc., Parsippany, NJ 07054-0622
©2009 4204 U.S. Patent No. 4,628,098
PREVACID® is a registered trademark of Takeda Pharmaceuticals North America, Inc.

34. The instances of false marking shown in paragraphs 31-33 are only representative and are not meant to be exhaustive.

35. When a patent expires, all prospective rights in the patent terminate irrevocably. Therefore, a product marked with an expired patent is not currently protected by such expired patent.

36. Defendant is a sophisticated company and has many decades of experience applying for, obtaining, and litigating patents.

37. Upon information and belief, Defendant has an in-house legal department.

38. Upon information and belief, attorneys in Defendant's in-house legal department are responsible for Defendant's intellectual property, including marketing, labeling, and advertising law.

39. Defendant (by itself or by its representatives) cannot genuinely believe that a patent does not expire or that prospective patent rights apply even after a patent's expiration.

40. Upon information and belief, Defendant knows, or should know (by itself or by its representatives), that the '098 Patent marked on the product packaging, package insert and advertisement for its Prevacid®24HR product has expired. In this regard, Defendant and its counsel are presumed to know the law, and are therefore presumed to be familiar with both the expiration dates of their patents and the laws against false marking.

41. The product packaging, package insert and advertisement for Defendant's Prevacid®24HR product each bear the following copyright notice: "© 2009." Upon information and belief, this copyright notice indicates that the layout and/or the contents of the product packaging, package insert and advertisement were created or last reviewed or revised some time after December 31, 2008.

42. As alleged in paragraph 18 above, Defendant and Takeda Pharmaceuticals partnered in making the prescription medicine Prevacid® available as an over-the-counter

treatment for frequent heartburn, now marketed by Defendant as Prevacid®24HR (*see* Exhibit B).

43. On May 25, 2007, Takeda Pharmaceuticals Company Limited ("Takeda") and TAP Pharmaceutical Products Inc. ("TAP")[3] filed a Patent Infringement law suit against Teva Pharmaceuticals USA, Inc. *et al.*, a generic drug manufacturer.[4] In its complaint, Takeda and TAP describe in great detail the original expiration date of the '098 Patent, the term extension granted by the USPTO, and the ultimate expiration date of May 10, 2009. (*see* Exhibit D at paragraphs 18-20).

44. Upon information and belief, at least due to its previous partnership with Takeda (*see* Exhibit B), Defendant knows, or should know (by itself or by its representatives), that its Prevacid®24HR product is not covered, and in fact, was **never** covered, by the expired '098 Patent marked on the product packaging, package insert and advertisement for its Prevacid®24HR product because an expired patent has no prospective patent rights.

45. Defendant has in the past been engaged in patent litigation.

46. As a sophisticated company with, upon information and belief, in-house attorneys who regularly litigate or oversee litigation of patent infringement cases and who regularly prosecute or oversee patent prosecution, Defendant knows, or reasonably should know, of the requirements of 35 U.S.C. §292.

47. The false patent marking for the Prevacid®24HR product is found on the product packaging, package insert and advertisement for its Prevacid®24HR product. (*See* paragraphs 31-33 above)

[3] Upon information and belief, at least in May 2007, TAP was a joint venture between Takeda Pharmaceuticals and Abbott Laboratories. Upon information and belief, TAP is now d/b/a Takeda Pharmaceuticals North America, Inc.
[4] *Takeda Pharmaceutical Company Limited, et al. v. Teva Pharmaceuticals USA, Inc., et al.* (1:07-cv-00331).

48. Upon information and belief, Defendant intentionally marks the product packaging, package insert and advertisement for its Prevacid®24HR with the expired ‘098 Patent for the purpose of deceiving the public into believing that something contained in or embodied in its Prevacid®24HR product is protected by the expired ‘098 patent.

49. Each false marking on the product packaging, package insert and advertisement for its Prevacid®24HR is likely to, or at least has the potential to, discourage or deter persons and companies from commercializing competing products.

50. Upon information and belief, Defendant has wrongfully and illegally advertised a patent right which it does not possess and, as a result, has benefitted commercially and financially by maintaining false statements of patent rights.

51. Upon information and belief, Defendant knows, or reasonably should know, that marking the product packaging, package insert and advertisement for its Prevacid®24HR product with false patent statements was and is illegal under Title 35 United States Code. At a minimum, Defendant had and has no reasonable basis to believe that its use of the false markings was or is proper or otherwise permitted under federal law.

52. Upon information and belief, Defendant’s marking of its Prevacid®24HR product with the expired ‘098 Patent, as described above and/or as will be further later evidenced, has wrongfully quelled competition with respect to such products to an immeasurable extent thereby causing harm to the United States in an amount which cannot be readily determined.

53. Upon information and belief, for at least the reasons set forth herein, Defendant has wrongfully and illegally advertised patent rights which it does not possess, and, as a result, has likely benefitted in gaining and maintaining its considerable market share with respect to the herein described Prevacid®24HR product in the market place.

54. For at least the reasons provided herein, and/or for reasons which will be later evidenced, each expired patent which is marked on a product contributes to causing harm to the United States and the general public.

55. Thus, each expired patent marked on a product, directly or on the packaging thereof, multiplied by the number of products and/or packaging materials on which it appears is a separate "offense" pursuant to 35 U.S.C. §292(a).

VI.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully requests that this Court enter judgment against Defendant as follows:

(a) A decree that Defendant has falsely marked products in violation of 35 U.S.C. §292;

(b) An award of monetary damages, pursuant to 35 U.S.C. § 292, in the form of a civil monetary fine of $500 per false marking "offense," or an alternative amount as determined by the Court, one half of which should be paid to the United States of America;

(c) An accounting for any falsely marked products not presented at trial and an award by the Court of additional damages for any such falsely marked products;

(d) All costs and fees incurred as a result of the prosecution of this action; and

(e) Such other and further relief, at law or in equity, to which Plaintiff is justly entitled.

VII.

DEMAND FOR JURY TRIAL

Pursuant to Federal Rules of Civil Procedure Rule 38, Plaintiff hereby demands a jury trial on all issues triable by jury.

Dated: November 9, 2010

Respectfully submitted,

PUBLIC PATENT FOUNDATION, INC.

By: / s Robert D. Cheifetz
One of its attorneys

Attorneys for Plaintiff

Joseph M. Vanek
IL State Bar No. 6197046
VANEK, VICKERS & MASINI, P.C.
111 S. Wacker Drive, Suite 4050
Chicago, Illinois 60606
(312) 224-1500 Telephone
(312) 224-1510 Facsimile
E-mail: jvanek@vaneklaw.com

Bruce S. Sperling
IL State Bar No. 2687925
Robert D. Cheifetz
IL State Bar No. 6210105
SPERLING & SLATER, P.C.
55 West Monroe Street
Suite 3200
Chicago, Illinois 60603
(312) 641-3200 Telephone
(312) 641-6492 Facsimile
E-mail: bss@sperling-law.com
E-mail: robc@sperling-law.com

Eugene M. Cummings
IL State Bar No. 556394

David Lesht
IL State Bar No. 6180985
Martin Goering
IL State Bar No. 6286254
EUGENE M. CUMMINGS, P.C.
One North Wacker Drive, Suite 4130
Chicago, Illinois 60606
(312) 984-0144 Telephone
(312) 984-0146 Facsimile
E-mail: ecummings@emcpc.com
E-mail: dlesht@emcpc.com
E-mail: mgoering@emcpc.com

OF COUNSEL:

Daniel B. Ravicher, Esq.
David Garrod, Ph.D., Esq.
PUBLIC PATENT FOUNDATION, INC.
Benjamin N. Cardozo School of Law
55 Fifth Avenue
New York, New York 10003
(212) 545-5337 Telephone
(212) 591-6038 Facsimile
E-mail: info@pubpat.org

Exhibit A

NOVARTIS

Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland
http://www.novartis.com

MEDIA RELEASE • COMMUNIQUÉ AUX MÉDIAS • MEDIENMITTEILUNG

Novartis launches Prevacid®24HR over-the-counter for full 24-hour frequent heartburn treatment

- *Prevacid®24HR prevents acid production that causes frequent heartburn pain for a full 24 hours with one pill a day*
- *Prevacid®24HR provides America's 50 million frequent heartburn sufferers[1] with convenient and easy accessibility to this effective heartburn treatment*
- *First new over-the-counter treatment for frequent heartburn sufferers in six years*

Click here for multimedia content

Basel, November 12, 2009 — Novartis announced the availability of Prevacid®24HR (lansoprazole delayed-release capsules 15 mg/acid reducer) over-the-counter in pharmacies and retail stores across the US to treat frequent heartburn. Prevacid®24HR received US Food and Drug Administration (FDA) approval in May 2009. It is the first and only over-the-counter (OTC) Proton Pump Inhibitor (PPI) for the treatment of frequent heartburn in its original formulation.

"It is well known that Americans are taking more ownership of their health-care decisions. The launch of Prevacid®24HR for the treatment of frequent heartburn is a milestone in the over-the-counter medicine category, expanding the treatment choices for the millions of adults who suffer from frequent heartburn," said Dirk Van de Put, Global Head, Over the Counter Business Unit, Novartis Consumer Health. "We're looking forward to providing frequent heartburn sufferers with broad access to this very effective treatment and expect the launch to drive strong incremental growth for the OTC Digestive Health category."

Prevacid® (lansoprazole)[2] was one of the most prescribed acid reducer brands in the US over the last decade[3] based on IMS Data. The same medicine in Prevacid is now available over-the-counter in Prevacid®24HR for the treatment of frequent heartburn. Frequent heartburn is defined as heartburn that occurs two or more days per week.

Prevacid®24HR is clinically proven to work for a full 24 hours, both day and night. It is the only PPI approved for OTC treatment of frequent heartburn that contains the active ingredient lansoprazole. Starting today, Prevacid®24HR is expected to be available in more than 100,000 pharmacies, drug stores, supermarkets, mass merchandisers and other retail locations throughout the US.

Prevacid®24HR is clinically proven to treat frequent heartburn
Prevacid®24HR prevents acid production that causes frequent heartburn pain for a full 24 hours, with one pill a day. Clinical study data shows that Prevacid®24HR provides frequent heartburn sufferers more heartburn-free days and nights than placebo[4,5]. Prevacid®24HR starts working early to treat frequent heartburn and maintains its

effectiveness for the full 14-day course of treatment. In two clinical trials, 88% of people who used Prevacid®24HR for frequent heartburn were satisfied[6].

In addition to Prevacid®24HR, Novartis Consumer Health, Inc. has demonstrated success with switching other prescription products over the counter, enabling more consumers to get access to the medicines they need, while continuing to build the brands. Three of the company's biggest and most successful global switches come from the Pharmaceuticals Division of Novartis AG – Voltaren®, Lamisil® and Nicotinell® and account for 30 percent of Novartis Consumer Health global sales.

Frequent heartburn significantly affects sufferers' quality of life

While frequent heartburn is a common condition, its impact on sufferers may be underestimated. According to the *Experience of Frequent Heartburn in America, 2009*[7], a national study of 1,075 frequent heartburn sufferers conducted by the Center for Health Outcomes Research & Evidence Based Medicine, LLC and United BioSource Corporation, frequent heartburn is not only painful, but can also significantly impact sufferers' quality of life. The study, conducted in consultation with leading physicians and gastroenterologists, was designed to measure and validate the quality of life impact that frequent heartburn currently can have on sufferers. It found that frequent heartburn can affect sufferers' ability to get a good night's sleep, be productive at work, have positive personal relationships and enjoy social activities. The study also showed that those with more severe frequent heartburn pain can experience a greater impact on their quality of life.

"Until now, frequent heartburn has been largely misunderstood in America. The data from this study confirms how frequent heartburn affects my patients' daily lives – it can interrupt sufferers' work, social activities and a full night's sleep," said Dr. Brian Fennerty, practicing gastroenterologist and professor of Medicine in the Division of Gastroenterology at Oregon Health & Science University in Portland, Oregon. "The over-the-counter availability of a proven molecule like lansoprazole provides choice and options to the millions of frequent heartburn sufferers and empowers them to treat their symptoms."

The study, which was funded by Novartis Consumer Health, Inc. revealed that[7]:

- About 75% of frequent heartburn sufferers experienced some sleep problems as a result of their heartburn – either problems falling asleep or staying asleep.
- Living with frequent heartburn pain can affect personal relationships, including social activities with family and friends, quality time with children and spouses, and even sexual relationships.
- For 52% of sufferers, discomfort from frequent heartburn has some impact on their work, including their ability to focus in meetings and their overall ability to be productive.

The study also found that reducing the frequency and severity of frequent heartburn pain could result in significant improvements in a sufferer's mood, relationships with family, productivity at work, diet and enjoyment of social activities[7]. Additional results of the study are available at www.Prevacid24HR.com.

As part of the launch of Prevacid®24HR, Novartis Consumer Health is partnering with Dr. Fennerty and MSN.com Lifestyle Expert Kelley Moore to educate the public about frequent heartburn and motivate them to take action. Through the Heartburn Action Plan, Dr. Fennerty and Ms. Moore will share treatment options and lifestyle tips that will help empower frequent heartburn sufferers to treat their symptoms. Log on to www.HeartburnActionPlan.com for more information.

About Frequent Heartburn

More than 50 million American adults suffer from frequent heartburn,[1] which is defined as heartburn occurring two or more days per week. Frequent heartburn is a result of the backing up of stomach acid into the esophagus. Typically the lower esophageal sphincter muscle opens to allow food to pass, but then quickly closes. However, in frequent heartburn sufferers, the muscle relaxes and allows food and acid from the stomach to travel back up into the esophagus. As a result, sufferers often have a burning sensation in the chest and/or throat, a sour or bitter taste in the mouth, difficulty swallowing, chronic coughing and wheezing or other asthma-like symptoms. These symptoms of frequent heartburn can become worse when one is lying down or bending over.

About Prevacid®24HR

Prevacid®24HR is now available over-the-counter to treat frequent heartburn for a full 24 hours with one pill a day. It received US Food and Drug Administration (FDA) approval in May 2009. It is the first and only over-the-counter PPI for the treatment of frequent heartburn in its original formulation.

Prevacid®24HR is clinically proven to work for a full 24 hours, both day and night. Although some people get complete relief of symptoms within 24 hours, it may take one to four days for full effect. Consumers should use Prevacid®24HR as directed for 14 days to treat their frequent heartburn and may take one 14-day course of treatment every four months, or as directed by their doctor. If their heartburn continues or worsens, they should stop use and ask a doctor.

Prevacid®24HR is expected to be available in more than 100,000 retail store locations nationwide, starting at an average retail price of $11.99.

For more information about Prevacid®24HR, including instructions for use, visit www.Prevacid24HR.com.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as "look forward to," "expect," "expected," "can," "could," "will," "may," or similar expressions, or by express or implied discussions regarding the potential date on which Prevacid®24HR will be available for sale over-the-counter, the extent of the distribution of Prevacid®24HR, or regarding potential future revenues from Prevacid®24HR. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with Prevacid®24HR to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Prevacid®24HR will be available for sale over-the-counter on any particular date. Nor can there be any guarantee regarding the extent of the distribution of Prevacid®24HR, or that Prevacid®24HR will achieve any particular levels of revenue in the future. In particular, management's expectations regarding Prevacid®24HR could be affected by, among other things, unexpected difficulties in manufacturing or distribution; competition in general; government, industry and general public pricing pressures; unexpected regulatory actions or government regulation generally; the impact that the foregoing factors could have on the values attributed to the Novartis Group's assets and liabilities as recorded in the Group's consolidated balance sheet, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis
Novartis provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on healthcare, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic pharmaceuticals, preventive vaccines, diagnostic tools and consumer health products. Novartis is the only company with leading positions in each of these areas. In 2008, the Group's continuing operations achieved net sales of USD 41.5 billion and net income of USD 8.2 billion. Approximately USD 7.2 billion was invested in R&D activities throughout the Group. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 99,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit http://www.novartis.com.

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References
1 National Heartburn Alliance: http://www.heartburnalliance.org/ heartburn_assessment.php
2 Prevacid® is a registered trademark of Takeda Pharmaceuticals North America, Inc., and is used under license by Takeda Pharmaceuticals North America, Inc.
3 Based on IMS Data of the total number of Prevacid® prescriptions from 1998 – 2008
4 Peura, DA et al. *Aliment Pharamcol Ther.* 2009; 30:459-468
5 Kushner PR, et al. *Postgrad Med.*2009; 121(4):67-75
6 Novartis Consumer Health, Inc. Data on file.
7 "The Experience of Frequent Heartburn in America, 2009" Research conducted by the Center for Health Outcomes Research & Evidence Based Medicine, LLC and United BioSource Corporation

Novartis Media Relations

Central media line : +41 61 324 2200

Eric Althoff
Novartis Global Media Relations
+41 61 324 7999 (direct)
+41 79 593 4202 (mobile)
eric.althoff@novartis.com

Julie Masow
Novartis Consumer Health, Inc.
+1 973 503 7663 (direct)
+1 862 579 8456 (mobile)
julie.masow@novartis.com

e-mail: media.relations@novartis.com

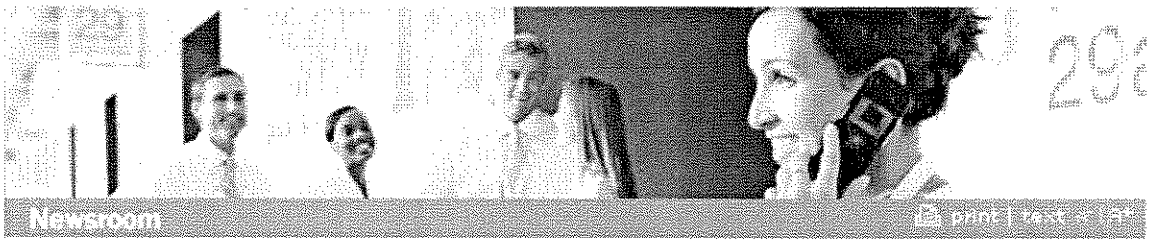
Novartis Investor Relations

Central phone:	+41 61 324 7944		
Ruth Metzler-Arnold	+41 61 324 9980	**North America:**	
Pierre-Michel Bringer	+41 61 324 1065	Richard Jarvis	+1 212 830 2433
John Gilardi	+41 61 324 3018	Jill Pozarek	+1 212 830 2445
Thomas Hungerbuehler	+41 61 324 8425	Edwin Valeriano	+1 212 830 2456
Isabella Zinck	+41 61 324 7188		

e-mail: investor.relations@novartis.com

e-mail: investor.relations@novartis.com

Exhibit B



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Novartis receives approval from FDA to market Prevacid®24HR as first and only OTC proton pump inhibitor in original formulation

This approval will provide greater convenience and broader access to an effective treatment option to the 50 million Americans[1] suffering from frequent heartburn

Once-daily Prevacid®24HR is the first OTC proton pump inhibitor approved for the treatment of frequent heartburn in the US since 2003

Prevacid®24HR treats frequent heartburn for a full 24 hours

Basel, Switzerland, May 14, 2009 - Novartis announced today that Prevacid®24HR (lansoprazole delayed-release capsules 15 mg) has been approved by the U.S. Food and Drug Administration (FDA) as the first over-the-counter (OTC) Proton Pump Inhibitor (PPI) for the treatment of frequent heartburn since 2003. Prevacid24HR is expected to be available over-the-counter in 2009.

Once-daily Prevacid24HR is the first OTC PPI approved in its original formulation. It is the only PPI containing the active ingredient lansoprazole to be approved for OTC treatment of frequent heartburn, which is defined as heartburn that occurs two or more days per week. In three clinical studies, Prevacid®24HR demonstrated significantly better efficacy in treating frequent heartburn than placebo. Although some people experienced complete relief of symptoms within 24 hours, it may take one to four days for full effect.

The prescription medicine Prevacid® (lansoprazole)[2], a brand that 21 million patients have trusted to treat their acid-related disorders[3], is one of the top five prescription brands in the U.S. in terms of total prescription dollar sales[4]. The drug achieved $3.37 billion in annual sales in the U.S. in 2008[5]. Novartis has licensed the Prevacid® trademark and certain other intellectual property rights for OTC development and commercialization from Takeda Pharmaceuticals North America, Inc.

"Our partnership with Takeda Pharmaceuticals on this switch has been outstanding," said Larry Allgaier, Global Head of the Novartis OTC Business Unit. "Takeda Pharmaceuticals trusted Novartis to take this leading product over-the-counter because of our core competencies as a pharmaceutical company, and our demonstrated history of success taking prescription products over the counter, providing consumers with greater convenience and broader access to the effective treatments they need, while continuing to build the brands."

Prevacid®24HR treats frequent heartburn for a full 24 hours. Prevacid®24HR works by stopping the release of acid into the stomach.

"This is an important development for the 50 million American adults who suffer from frequent heartburn," said M. Brian Fennerty, MD, Professor of Medicine, Division of Gastroenterology, Oregon Health and Science University. "Prevacid®24HR will be both an effective and well-tolerated option for treating frequent heartburn."

The FDA approved Prevacid®24HR in the form of 15mg delayed-release capsules. Prevacid®24HR is a 14-day course of treatment and should be taken once per day before eating in the morning to treat frequent heartburn.

For more information about Prevacid®24HR visit www.Prevacid24HR.com.

About Frequent Heartburn

More than 50 million Americans suffer from frequent heartburn, which is defined as heartburn occurring two or more days per week. Frequent heartburn is a result of the backing up of stomach acid into the esophagus. Typically the lower esophageal sphincter muscle opens to allow food to pass, but then quickly closes. However, in frequent heartburn sufferers the muscle relaxes and allows food and acid from the stomach to travel back up into the esophagus. As a result, sufferers often have a burning sensation in the chest and/or throat, a sour or bitter taste in the mouth, difficulty swallowing, chronic coughing and wheezing or other asthma-like symptoms. These symptoms of frequent heartburn can become worse when one is lying down or bending over.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as "will," "expected," or similar expressions, or by express or implied discussions regarding the potential date on which Prevacid®24HR will be available for sale over-the-counter or regarding potential future revenues from Prevacid®24HR. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with Prevacid®24HR to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Prevacid®24HR will be available for sale over-the-counter on any particular date. Nor can there be any guarantee that Prevacid®24HR will achieve any particular levels of revenue in the future. In particular, management's expectations regarding Prevacid®24HR could be affected by, among other things, competition in general; government, industry and general public pricing pressures; unexpected regulatory actions or government regulation generally; the impact that the foregoing factors could have on the values attributed to the Novartis Group's assets and liabilities as recorded in the Group's consolidated balance sheet, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

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# # #

References

[1] National Heartburn Alliance: http://www.heartburnalliance.org/heartburn_assessment.php

[2] Prevacid® is a registered trademark of Takeda Pharmaceuticals North America, Inc., and is used under license by Takeda Pharmaceuticals North America, Inc.

[3] SDI Total Patient Tracker (TPT) 2002-2008

[4] SDI VONA 12-months ending December 31, 2008

[5] IMS NPA 12-months ending December 31st, 2008

Novartis Media Relations

Central media line : +41 61 324 2200

Eric Althoff
Novartis Global Media Relations
+41 61 324 7999 (direct)

Julie Masow
Novartis Consumer Health, Inc.
+1 973 503 7663 (direct)

+41 79 593 4202 (mobile)
eric.althoff@novartis.com

+1 862 579 8456 (mobile)
julie.masow@novartis.com

e-mail: media.relations@novartis.com

Novartis Investor Relations

Central phone:	+41 61 324 7944		
Ruth Metzler-Arnold	+41 61 324 9980	**North America:**	
Pierre-Michel Bringer	+41 61 324 1065	Richard Jarvis	+1 212 830 2433
John Gilardi	+41 61 324 3018	Jill Pozarek	+1 212 830 2445
Thomas Hungerbuehler	+41 61 324 8425	Edwin Valeriano	+1 212 830 2456
Isabella Zinck	+41 61 324 7188		

e-mail: investor.relations@novartis.com

e-mail: investor.relations@novartis.com

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Exhibit C

United States Patent [19]

Nohara et al.

[11] **Patent Number: 4,628,098**

[45] **Date of Patent: Dec. 9, 1986**

[54] **2-[2-PYRIDYLMETHYLTHIO-(SULFINYL)-]BENZIMIDAZOLES**

[75] Inventors: **Akira Nohara; Yoshitaka Maki,** both of Kyoto, Japan

[73] Assignee: **Takeda Chemical Industries, Ltd.,** Osaka, Japan

[21] Appl. No.: **760,568**

[22] Filed: **Jul. 29, 1985**

[30] **Foreign Application Priority Data**

Aug. 16, 1984 [JP] Japan 59-171069

[51] **Int. Cl.**[4] **C07D 401/12**

[52] **U.S. Cl.** **546/271**

[58] **Field of Search** 546/271

[56] **References Cited**

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FOREIGN PATENT DOCUMENTS

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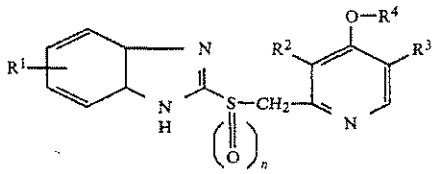
2134523A	8/1984	United Kingdom .

Primary Examiner—Jane T. Fan

Attorney, Agent, or Firm—Wegner & Bretschneider

[57] **ABSTRACT**

The compound of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, or a pharmacologically acceptable salt thereof is novel, and useful for prophylaxis and therapy of digestive ulcers (e.g. gastric ulcer, duodenal ulcer) and gastritis.

36 Claims, No Drawings

2-[2-PYRIDYLMETHYLTHIO-(SULFINYL)]BENZIMIDAZOLES

This invention relates to pyridine derivatives useful as e.g. anti-ulcer agents and to a method of preparing them.

As the pyridine derivatives having anti-ulcer activity, those disclosed in U.S. Pat. No. 4,255,431 (Japanese Unexamined Patent Laid-open No. 141783/79) and U.S. Pat. No. 4,472,409 (Japanese Unexamined Patent Laid-open No. 135881/83) etc. have been known.

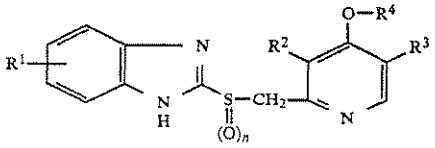
However, while these known compounds have an acid-secretion-inhibiting action, their gastric mucous membrane protecting action is insufficient, thus being hardly considered satisfactory as anti-ulcer agents. Besides, these compounds are possessed of such drawbacks in the physico-chemical properties as being unstable and readily decomposed.

It is considered that gastrointestinal ulcer is induced by unbalance between aggressive factors, e.g. hydrochloric acid, pepsin, and defensive factors, e.g. mucus secretion and mucosal blood flow. Therefore, a medicine having both an action of inhibiting gastric acid secretion and an action of enhancing protection of gastric mucosa has been desired.

The present inventors diligently studied with the purpose of preparing an anti-ulcer agent having excellent actions of inhibiting gastric acid secretion, of protecting gastric mucosa and of antagonizing ulceration. They found that a certain type of pyridine derivatives meets the said purpose, and they conducted further study to accomplish the present invention.

The present invention relates to

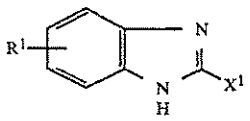
(1) pyridine derivatives of the formula (I)



(I)

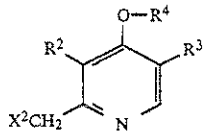
wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl, and n denotes 0 or 1, or their pharmacologically acceptable salts and

(2) a method for preparing a compound (I) or its pharmacologically acceptable salt, which comprises allowing a compound of the formula (II)



(II)

wherein R^1 is of the same meaning as defined above, to react with a compound of the formula (III)



(III)

wherein R^2, R^3 and R^4 are of the same meaning as defined above, one of X^1 and X^2 is SH and the other is a leaving group and, when necessary, by subjecting the reaction product to oxidation.

In the above formulae, C_{2-5} fluorinated alkyl groups shown by R^4 are exemplified by 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, 2,2,3,3-tetrafluoropropyl 1-(trifluoromethyl)-2,2,2-trifluoroethyl, 2,2,3,3,4,4,4-heptafluorobutyl and 2,2,3,3,4,4,5,5-octafluoropentyl.

Examples of the leaving groups X^1 and X^2 in the above formulae are halogen, preferably chlorine, bromine or iodine, or a reactive esterified hydroxy group, e.g. an arylsulfonyloxy, for example, phenylsulfonyloxy or tosyloxy, or C_{1-4} alkylsulfonyloxy, for example, methanesulfonyloxy, or an organic phosphoryloxy, for example, diphenylphosphoryloxy, dibenzylphosphoryloxy or di-C_{1-4}alkylphosphoryloxy and the like.

R^1 may be located at 4- or 5-position, and preferably at 5-position.

A sulfide derivative (I) (n=0), among the object compounds of this invention, can be prepared by allowing a compound (II) to react with a compound (III). It is convenient to conduct this reaction in the presence of a base. The base is exemplified by alkali metal hydride e.g. sodium hydride and potassium hydride; alkali metal e.g. metallic sodium; sodium alcoholate e.g. sodium methoxide and sodium ethoxide; alkali metal carbonate e.g. potassium carbonate and sodium carbonate; and organic amines e.g. triethylamine. The solvent used for the reaction is exemplified by alcohols e.g. methanol and ethanol, as well as dimethylformamide. The amount of a base used for the reaction is usually in a little excess to the equivalent, but it may be in a large excess. Specifically, it is about 1–10 equivalents, more preferably about 1–equivalents. The reaction temperature ranges usually from about 0° C. to about the boiling point of the solvent then used, more preferably from about 20° C. to about 80° C. The reaction time ranges from about 0.2 to about 24 hours, more preferably from about 0.5 to about 2 hours.

A sulfinyl derivative (I) (n=1), which is also among the object compounds of this invention, can be prepared by subjecting a compound (I) (n=0) to oxidation. The oxidizing agent to be employed here is exemplified by peracid e.g. m-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid and permaleic acid, or sodium bromite or sodium hypochlorite or hydrogen peroxide. The solvent used for the reaction is exemplified by halogenated hydrocarbon e.g. chloroform and dichloromethane, ethers e.g. tetrahydrofuran and dioxane, amides e.g. dimethylformamide, alcohols, e.g. methanol, ethanol, propanol, and t-butanol or water, and these solvents may used singly or in admixture. The oxidizing agent is used preferably in approximately equivalent or a little excess amount relative to the compound (I) (n=0). Specifically, it is about 1 to about 3 equivalents, more preferably about 1–1.5 equivalent. The reaction temperature ranges from that under ice-cooling to about the boiling point of the solvent then employed, usually from that under ice-cooling to room temperature, more preferably from about 0° C. to about 10° C. The reaction time usually ranges from about 0.1 to about 24 hours, more preferably from about 0.1 to about 4 hours.

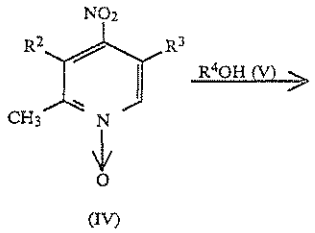
The object compound (I) produced by the above reaction can be isolated and purified by conventional means e.g. recrystallization and chromatography.

The compound (I) of this invention may be led to pharmacologically acceptable salts thereof by per se conventional means, the salts being exemplified by hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate.

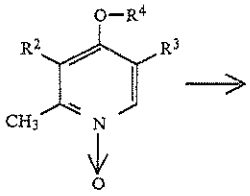
Among the compounds (I), those of n=0 give stable salts, while those of n=1 may exist as an aqueous solution though unstable.

The process of preparing the starting material (III) is described as follows.

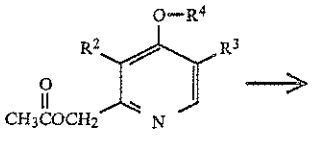
(Process 1)



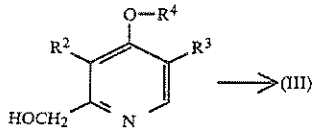
(IV)



(VI)



(VII)



(VIII)

A nitro compound of the formula (IV) [wherein R^2 and R^3 are of the same meaning as defined above] is allowed to react with an alcohol derivative R^4OH (V) [wherein R^4 is of the same meaning as defined above] in the presence of a base to give an alkoxy derivative of the formula (VI) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The base is exemplified by alkali metal e.g. lithium, sodium and potassium; alkali metal hydride e.g. sodium hydride and potassium hydride; alcoholate e.g. potassium t-butoxide and sodium propoxide; alkali metal carbonate or hydrogen carbonate e.g. potassium carbonate, lithium carbonate, sodium carbonate, potassium hydrogen carbonate and sodium hydrogen carbonate; or alkali hydroxide e.g. sodium hydroxide and potassium hydroxide. The solvent used for the reaction is exemplified by, besides R^4OH itself, ethers such as tetrahydrofuran and dioxane as well as ketones such as acetone and methyl ethyl ketone, acetonitrile, dimethylformamide and hexamethylphosphoric acid triamide. The reaction temperature is suitably selected within the range from those under ice-cooling to those near the boiling point of the solvent used. The reaction time ranges usually from about 1 to about 48 hours.

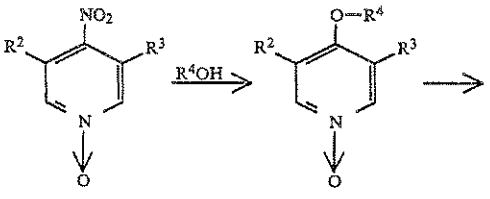
The thus-obtained compound (VI) is subjected to heating (about 80° to about 120° C.) in the presence of acetic anhydride singly or together with a mineral acid e.g. sulfuric acid and perchloric acid to give a 2-acetoxymethylpyridine derivative of the formula (VII) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The reaction time ranges usually from about 0.1 to about 10 hours.

Then, the compound (VII) is subjected to alkali-hydrolysis to give a 2-hydroxymethyl pyridine derivative of the formula (VIII) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The alkali is exemplified by sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate. The solvent used for the reaction is exemplified by methanol, ethanol and water. The reaction temperature ranges usually from about 20° C. to about 60° C. The reaction time is within the range of from about 0.1 to about 2 hours.

The compound (VIII) is further subjected to reaction with a chlorinating agent such as thionyl chloride, or an esterifying agent, e.g. an organic sulfonic acid chloride such as methanesulfonyl chloride or p-toluenesulfonyl chloride, or an organic phosphoric acid chloride such as diphenylphosphoryl chloride to give the compound (III). The amount of the chlorinating agent used for the reaction is usually in equivalent to a large excess relative to the compound (VIII). The solvent used for the reaction is exemplified by chloroform, dichloromethane and tetrachloroethane. The reaction temperature is usually within the range of from about 20° C. to about 80° C., and the reaction time is about 0.1 to about 2 hours.

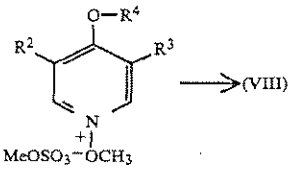
The amount of the organic sulfonic acid chloride or organic phosphoric acid chloride used for the reaction is usually in equivalent to a little excess, and the reaction is usually conducted in the presence of a base. The base is exemplified by organic base e.g. triethylamine and tributylamine, or inorganic base e.g. sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The amount of a base used for the reaction is usually in equivalent to a little excess. The solvent used for the reaction is exemplified by chloroform, dichloromethane, carbon tetrachloride or acetonitrile. The reaction temperature ranges usually from that under ice-cooling to about the boiling point of the solvent then used. The raction time ranges usually from a few minutes to a few hours. It is usually preferable to use the thus-produced compound (III) immediately for the reaction with a compound (II).

(Process 2)



(IX) (X)

-continued



(XI)

By a reaction similar to the above-described process (I), a compound of the formula (IX) [wherein R^2 and R^3 are of the same meaning as defined above] is led to a compound of the formula (X) [wherein R^2, R^3 and R^4 are of the same meaning as defined above].

Then, the compound (X) is subjected to methylation with dimethyl sulfate to give a compound of the formula (XI) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The reaction can be conducted usually without solvent. The reaction temperature ranges from about 100° C. to about 120° C., and the reaction time is within the range of from about 0.1 to about 4 hours.

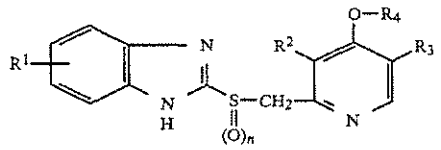
Further, the compound (XI) is allowed to react with a radical source such as ammonium persulfate or any other persulfate in methanol to give the above-mentioned compound (VIII). The reaction temperature is within the range of from about 20° C. to about 80° C., and the reaction time ranges from about 0.5 to about 4 hours.

Pharmacological actions of the compounds of the present invention are described as follows.

As the models of gastrointestinal ulcers, restraint and water-immersion stress-induced ulcer, indomethacin-induced ulcer and ethanol-induced gastric mucosal lesions have been used. However, as a model mimicking human gastric ulcer, indomethacin-induced gastric antral ulcer was reported in "Gastroenterology" (Satoh et al. 81, p. 719, 1981), which is considered to be of value as an experimental model. Therefore, the following are data of anti-ulcer actions of the object compounds (I) and of some representable known compounds, on the ulcer model in the above-mentioned literature reference. Experimental Method:

Male Sprague-Dawley rats of 7-weeks old were fasted for 24 hours. These animals were administered test compounds into stomach by using a gastric tube. After 30 minutes, indomethacin, 30 mg/kg subcutaneously, was administered. During 30–90 minutes after the administration of indomethacin, these animals had free access to chow pellets (Japan Clea, CE-2). At 5 hours after the administration of indomethacin, 1 ml of 1% Evans blue was injected to the animals via the tail vein, followed by sacrificing these animals with carbon dioxide gas. The stomach was removed together with the lower part of esophagus and the duodenum. The esophagus was clipped, 10 ml of 1% formalin solution was instilled into the stomach from the duodenum, and then the duodenum was clipped. The whole stomach waa immersed in 1% formalin solution. About 15 minutes later, the stomachs were opened along the greater curvature. The area of the lesions which occurred in the gastric antral mucosa was measured under a dissecting microscope with a square-grid eye piece (x10). The sum total of the individual lesions in each animal was measured, and the average value per group was calculated. Based on the difference between the average value of each group and that of the control group, the inhibition rate was determined. The test compound and indometachacin were suspended in a 5% gum arabic solution, respectively and administered in a volume of 2 ml/kg.

Experimental Results:



R^1	R^2	R^3	R^4	n	Anti-ulcer action[a] ID_{50} (mg/kg, p.o.)
H	H	H	CH_2CF_3	1	2.4
H	CH_3	H	CH_2CF_3	1	<1.0
H	H	H	$CH_2CF_2CF_3$	1	1.3
H	CH_3	H	$CH_2CF_2CF_3$	1	<1.0
H	H	H	$CH_2CF_2CF_2H$	1	1.3
H	CH_3	H	$CH_2CF_2CF_2H$	1	<1.0
H	CH_3	H	$CH_2CF_2CF_3$	0	3.7
5-OCH_3	CH_3	CH_3	CH_3*1		21.0
5-CF_3	CH_3	H	CH_3*2		5.5

*1The compound disclosed in Example 23 of USP. 4,255,431 (Japanese Unexamined Patent Laid-open No. 141783/1979)

*2The compound disclosed in Example 3 of USP. 4,472,409 (Japanese Unexamined Patent Laid-open No. 135881/1983)

[a]Using 6 rats per group, each of the test compounds was administered in a dose of 1, 3, 10 and 30 mg/kg to determine ID_{50}.

As shown by the above data, the compounds of this invention have superior anti-ulcer action as compared with known compounds by about 1.5–20 times or more. Besides, the compound (I) of this invention shows excellent actions of inhibiting gastric acid secretion, protecting gastric mucous membrane and preventing ulceration.

Regarding about the toxicity of the compound (I) of this invention, oral administration of the compound employed for the experiment of anti-ulceration (compound of R^1=H, R^2=CH_3, R^3=H, R^4=$CH_2CF_2CF_3$, n=1) to mice even in a dose of 2000 mg/kg caused no fatal effect; thus the compound (I) is low in toxicity.

As described in the foregoing, the compound (I) of this invention has an anti-ulcer action, a gastric acid secretion controlling action and a mucous membrane protecting action, furthermore is of low toxicity and is relatively stable as a chemical substance. The compound (I) of this invention can thus be used for prophylaxis and therapy of digestive ulcers (e.g. gastric ulcer, duodenal ulcer) and gastritis in mammalian animals (e.g. mouse, rat, rabbit, dog, cat and man).

When the compound (I) of this invention is used as an anti-ulcer agent for the therapy of digestive ulcers in mammalian animals, it can be administered orally in a dosage form of capsules, tablets, granules, etc. by formulating with a pharmacologically acceptable carrier, excipient, diluent, etc. The daily dose is about 0.01–30 mg/kg, more preferably about 0.1–3 mg/kg.

Incidentally, the compound of this invention (I) (n=0) is useful as a starting material for preparing the compound (I) (n=1).

The processes of producing the starting compounds to be employed in the method of this invention as well as those of producing the compound (I) of this invention are specifically explained by the following Reference Examples and Working Examples.

REFERENCE EXAMPLE 1

In 2,2,3,3-tetrafluoropropanol (10 ml) was dissolved 2,3-dimethyl-4-nitropyridine-1-oxide (2 g). To the solution was added potassium t-butoxide (1.6 g) little by little at room temperature. The mixture was then heated at 80°–90° C. for 22 hours. The reaction solution was diluted with water, which was subjected to extraction with chloroform. The extract was dried on magnesium sulfate, and then concentrated. The concentrate was chromatographed on a column of silica gel (70 g). Elution was conducted with methanol-chloroform (1:10), and then subjected to recrystallization from ethyl acetate-hexane to yield 2.6 g of 2,3-dimethyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine-1-oxide as colorless needles, m.p. 138°–139° C.

After the manner above, compounds (VI) were prepared from compounds (IV).

Compound (VI)			
R^2	R^3	R^4	Melting point (°C.)
H	H	CH_2CF_3	148–150
CH_3	CH_3	CH_2CF_3	138–139

REFERENCE EXAMPLE 2

A mixture of 2,3-dimethyl-4-nitropyridine-1-oxide (2.0 g), methyl ethyl ketone (30 ml), 2,2,3,3,3-pentafluoropropanol (3.05 ml), anhydrous potassium carbonate (3.29 g) and hexamethyl phosphoric acid triamide (2.07 g) was heated at 70°–80° C. for 4.5 days under stirring, then insolubles were filtered off. The filtrate was concentrated, to which was added water. The mixture was subjected to extraction with ethyl acetate. The extract solution was dried on magnesium sulfate, followed by removing the solvent by evaporation. The residue was chromatographed on a column of silica gel (50 g), eluted with chloroform-methanol (10:1), and recrystallized from ethyl acetate-hexane to yield 2.4 g of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as colorless needles, m.p. 148°–149° C.

By this process, compounds (VI) were prepared from starting compounds (IV).

Compound (VI)			
R^2	R^3	R^4	Melting point (°C.)
CH_3	H	CH_2CF_3	131.0–131.5
H	CH_3	CH_2CF_3	153–154
H	H	$CH_2CF_2CF_3$	79–81
H	CH_3	$CH_2CF_2CF_3$	140–142
H	H	$CH_2CF_2CF_2H$	Oily
H	CH_3	$CH_2CF_2CF_2H$	143.5–144.5
CH_3	H	$CH_2CF_2CF_2H$	138–139

REFERENCE EXAMPLE 3

Concentrated sulfuric acid (two drops) was added to a solution of 2,3-dimethyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine-1-oxide (2.6 g) in acetic anhydride (8 ml). The mixture was stirred at 110° C. for 4 hours, which was then concentrated. The residue was dissolved in methanol (20 ml), to which was added sodium hydroxide (1.2 g) dissolved in water (5 ml). The mixture was stirred at room temperature for 30 minutes, which was concentrated. To the residue was added water, and the mixture was subjected to extraction with ethyl acetate. The extract was dried on magnesium sulfate, followed by removal of the solvent by evaporation. The residue was chromatographed on a column of silica gel (50 g), eluted with chloroform-methanol (10:1), and recrystallized from isopropyl ether to yield 1.6 g of 2-hydroxymethyl-3-methyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine as yellow crystals, m.p. 67°–68° C.

By this process, compounds (VIII) were prepared from compounds (VI).

Compound (VIII)			
R^2	R^3	R^4	Melting point (°C.)
H	H	CH_2CF_3	Oily
CH_3	H	CH_2CF_3	93.5–94.0
H	H	$CH_2CF_2CF_3$	Oily
CH_3	H	$CH_2CF_2CF_3$	Oily
H	CH_3	$CH_2CF_2CF_3$	87–89
H	H	$CH_2CF_2CF_2H$	88–89
H	CH_3	$CH_2CF_2CF_2H$	98–99
CH_3	H	$CH_2CF_2CF_2H$	67–68

REFERENCE EXAMPLE 4

To a solution of 3,5-dimethyl-4-nitropyridine-1-oxide (2.0 g) in 2,2,3,3,3-pentafluoropropanol (10 g) was added at 0° C. little by little potassium t-butoxide (2 g) over 15 minutes. The mixture was stirred at 60° C. for 18 hours. To the reaction mixture was added chloroform, which was subjected to filtration with celite. The filtrate was chromatographed on a column of silica gel (80 g), eluted with ethyl acetate-hexane (1:1), then with 20% methanol-ethyl acetate, and recrystallized from ether-hexane to yield 2.6 g of 3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as crystals, m.p. 89°–91° C.

By this process, compounds (X) were prepared from compounds (IX).

Compound (X)			
R^2	R^3	R^4	Melting point (°C.)
CH_3	H	CH_2CF_3	82–94
CH_3	CH_3	CH_2CF_3	138–139

REFERENCE EXAMPLE 5

A mixture of 3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide (2.5 g) and dimethyl sulfate (1 ml) was heated at 120° C. for 30 minutes, to which was then added methanol (12.5 ml). To the mixture was added dropwise at 80° C. ammonium persulfate (4.3 g) dissolved in water (20 ml)-methanol (10 ml) over 30 minutes, which was stirred for further 30 minutes. The resultant solution was concentrated. To the residue was added ice, which was neutralized with sodium carbonate, followed by extraction with chloroform. The extract was dried on sodium sulfate, followed by removing the solvent by evaporation to give 2.2 g of 3,5-dimethyl-2-hydroxymethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine as an oily substance.

By this process, compounds (VIII) were prepared from compounds (X).

Compound (VIII)			
R^2	R^3	R^4	Melting point (°C.)
H	CH_3	CH_2CF_3	116–119
CH_3	CH_3	CH_2CF_3	62–63

EXAMPLE 1

To a solution of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine (350 mg) in chloroform (10 ml) was added thionyl chloride (0.2 ml). The mixture was refluxed for 30 minutes, which was then concentrated. The residue was dissolved in methanol (5 ml). The solution was added to a mixture of 2-mercaptobenzimidazole (200 mg), 28% sodium methoxide solution (1 ml) and methanol (6 ml), which was refluxed for 30 minutes. From the resultant was removed methanol by evaporation. To the residue was added water, which was subjected to extraction with ethyl acetate. The extract was washed with a dilute sodium hydroxide solution, followed by drying on magnesium sulfate. From the resultant was removed the solvent by evaporation. The residue was then chromatographed on a column of silica gel (20 g), eluted with ethyl acetate-hexane (2:1), and then recrystallized from ethyl acetate-hexane to yield 370 mg of 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.½ hydrate as colorless plates, m.p. 145°–146° C.

By this process, compounds (I) (n=0) were prepared by allowing compounds (II) to react with compounds (III).

Compound (I) (n = 0)				
R^1	R^2	R^3	R^4	Melting point (°C.)
H	H	H	CH_2CF_3	138–139
H	CH_3	H	CH_2CF_3	149–150
H	H	CH_3	CH_2CF_3	168–170
H	CH_3	CH_3	CH_2CF_3	151.5–152.0
H	H	H	$CH_2CF_2CF_3$	125–126
H	H	CH_3	$CH_2CF_2CF_3$	151–152
H	H	H	$CH_2CF_2CF_2H$	Oily*3
H	CH_3	H	$CH_2CF_2CF_2H$	134–135
H	H	CH_3	$CH_2CF_2CF_2H$	148–149
H	CH_3	CH_3	$CH_2CF_2CF_3$	158–160
*4 5-CF_3	CH_3	H	CH_2CF_3	92–93
5-OCH_3	CH_3	H	CH_2CF_3	159–160
5-OCH_3	H	H	CH_2CF_3	152–153

*3NMR spectrum ($CDCl_3$)δ: 4.35(S), 4.39 (t,t,J=1.5 and 12 Hz), 5.98 (1H,t,t,J=52.5 and 4 Hz), 6.81 (1H,d,d,J=2 and 6 Hz) 6.95 (1H,d,J=2Hz), 7.1–7.3 (2H,m), 7.4–7.7 (2H,m), 8.50 (1H,d,J=6 Hz)
*4½H_2O (crystal water)

EXAMPLE 2

To a solution of 2-[3-methyl-4-(2,2,3,3,3,-pentafluoropropoxy)pyrid-2-yl-methylthiobenzimidazole (2.2 g) in chloroform (20 ml) was added dropwise under ice-cooling over a period of 30 minutes m-chloroperbenzoic acid (1.3 g) dissolved in chloroform (15 ml). The solution was washed with a saturated aqueous solution of sodium hydrogen carbonate, then dried on magnesium sulfate, and concentrated. The residue was chromatographed on a column of silica gel (50 g), eluted with ethyl acetate, and then recrystallized from aceton-isopropyl ether to give 1.78 g of 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropxy)pyrid-2-yl]methylsulfinylbenzimidazole as pale yellow prisms, m.p. 161°–163° C. (decomp.).

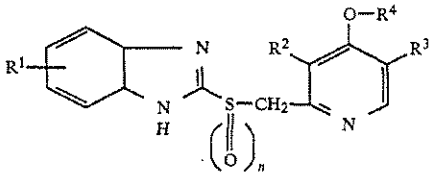
By this process, compounds (I) (n=1) were prepared from compounds (I) (n=0).

Compound (I) (n = 1)				
R^1	R^2	R^3	R^4	Melting point (°C.)
H	H	H	CH_2CF_3	176–177
H	CH_3	H	CH_2CF_3	178–182(d)
H	H	CH_3	CH_2CF_3	175–177(d)
H	CH_3	CH_3	CH_2CF_3	177–178(d)
H	H	H	$CH_2CF_2CF_3$	148–150(d)
H	H	CH_3	$CH_2CF_2CF_3$	145–148(d)
H	H	H	$CH_2CF_2CF_2H$	132–133
H	CH_3	H	$CH_2CF_2CF_2H$	147–148(d)
H	H	CH_3	$CH_2CF_2CF_2H$	136–139(d)
H	CH_3	CH_3	$CH_2CF_2CF_3$	157–159
5-CF_3	CH_3	H	CH_2CF_3	161–162(d)
5-OCH_3	CH_3	H	CH_2CF_3	140.5–142(d)
5-OCH_3	H	H	CH_2CF_3	162–163(d)

(Note) (d): decomposition

What we claim is:

1. A compound of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, and a pharmacologically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 is hydrogen.

3. A compound according to claim 1, wherein R^1 is methoxy.

4. A compound according to claim 1, wherein R^2 is hydrogen.

5. A compound according to claim 1, wherein R^2 is methyl.

6. A compound according to claim 1, wherein R^3 is hydrogen.

7. A compound according to claim 1, wherein R^3 is methyl.

8. A compound according to claim 1, wherein R^4 is a C_{2-3} fluorinated alkyl.

9. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

10. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

11. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-5-methyl-pyrid-2-yl]methylsulfinylbenzimidazole.

12. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-5-methyl-pyrid-2-yl]methylsulfinylbenzimidazole.

13. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

14. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3,3-pentafluoropropoxy)-5-methyl-pyrid-2-yl]methylsulfinylbenzimidazole.

15. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

16. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

17. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

18. A compound according to claim 1, wherein the compound is 2-[5-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

19. A compound according to claim 1, wherein the compound is 2-[3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

20. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinyl-5-trifluoromethylbenzimidazole.

21. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinyl-5-methoxybenzimidazole.

22. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]-methylsulfinyl-5-methoxybenzimidazole.

23. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]-methylthiobenzimidazole.

24. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylthiobenzimidazole.

25. A compound according to claim 1, wherein the compound is 2-[5-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylthiobenzimidazole.

26. A compound according to claim 1, wherein the compound is 2-[3,5-dimethyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylthiobenzimidazole.

27. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

28. A compound according to claim 1, wherein the compound is 2-[5-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

29. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

30. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

31. A compound according to claim 1, wherein the compound is 2-[5-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

32. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

33. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-5-methyl-pyrid-2-yl]methylthiobenzimidazole.

34. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl-methylthio-5-trifluoromethylbenzimidazole.

35. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl-methylthio-5-methoxybenzimidazole.

36. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylthio-5-methoxybenzimidazole.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

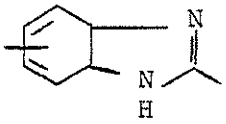
CERTIFICATE OF CORRECTION

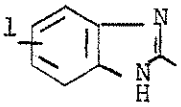
PATENT NO. : 4,628,098

DATED : December 9, 1986 Page 1 of 2

INVENTOR(S) : Akira NOHARA et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below: On the title page:

In the Abstract delete "  "

and insert --  --.

In column 1, line 40, delete " (O)n" and insert --  n--.

In column 4, line 52, delete "raction" and insert --reaction--.

In column 6, line 10, delete " (O)n and insert --  n--.

In column 9, line 49, delete "pyrid-2-yl-methyl" and insert --pyrid-2-yl]methyl--.

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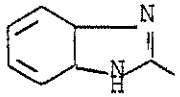
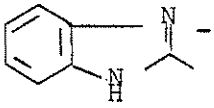
INVENTOR(S) : Akira NOHARA et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 10, line 23, claim 1, delete "R^1  " and insert --R^1  --.

Signed and Sealed this

Twelfth Day of April, 1988

Attest:

DONALD J. QUIGG

Attesting Officer

Commissioner of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

PATENT NO.	:	4,628,098
ISSUED	:	December 9, 1986
INVENTOR(S)	:	Akira Nohara et al.
PATENT OWNER	:	Takeda Chemical Industries Ltd.

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

1381 days

from the original expiration date of the patent, July 29, 2005, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 6th day of January 1997.

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE

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Exhibit D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICAL COMPANY LIMITED, a Japanese Corporation, TAP PHARMACEUTICAL PRODUCTS INC., a Delaware Corporation, and ETHYPHARM, S.A., a French Corporation,	)	
Plaintiffs,	)	
v.	)	C.A. No. _____
TEVA PHARMACEUTICALS USA, INC., a Delaware Corporation, and TEVA PHARMACEUTICAL INDUSTRIES LTD., an Israeli Corporation,	)	
Defendants.	)	

COMPLAINT

Plaintiffs Takeda Pharmaceutical Company Limited, TAP Pharmaceutical Products Inc., and Ethypharm, S.A. (collectively, "Plaintiffs"), as and for their Complaint against defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. (collectively "Defendants"), allege as follows:

THE PARTIES

1. Plaintiff Takeda Pharmaceutical Company Limited ("Takeda") is a Japanese corporation, having a principal place of business at 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan. As part of its business, Takeda is involved in the research, development, and marketing of pharmaceutical products.

2. Plaintiff TAP Pharmaceutical Products Inc. ("TAP") is a Delaware corporation, having a principal place of business at 675 North Field Drive, Lake Forest, Illinois

60045. As part of its business, TAP is involved in the research, development, and marketing of pharmaceutical products.

3. Plaintiff Ethypharm, S.A. ("Ethypharm") is a French corporation, having a principal place of business at 21 rue Saint Matthieu 78550, Houdan, France. As part of its business, Ethypharm is involved in the research, development, manufacturing, and licensing of pharmaceutical products. Ethypharm appears as a plaintiff in this action solely by virtue of being the record owner of U.S. Patent No. 5,464,632 ("the '632 Patent"). Ethypharm seeks relief in this action solely in respect to the '632 Patent.

4. On information and belief, defendant Teva Pharmaceuticals USA, Inc. ("Teva USA") is a Delaware corporation, having a principal place of business located at 1090 Horsham Road, North Wales, Pennsylvania 19454 and is engaged in the manufacture and sale of pharmaceutical products.

5. On information and belief, defendant Teva Pharmaceuticals Industries, Ltd. ("Teva Industries") is an Israeli corporation, having a principal place of business located at 5 Basel St., Petach Tikva 49131, Israel. On information and belief, Teva Industries manufactures bulk pharmaceutical products.

6. On information and belief, Teva Industries owns 100% of the ownership and voting interest in Teva USA.

7. On information and belief, Teva USA is controlled and/or dominated by Teva Industries.

8. On information and belief, Teva Industries conducts its North American operations, in part, through Teva USA.

JURISDICTION AND VENUE

9. This action arises under the patent laws of the United States of America, Title 35, United States Code. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

10. Teva USA is subject to personal jurisdiction in this District by virtue of, *inter alia*, its incorporation in Delaware, its conduct of business in this District, its purposeful availment of the rights and benefits of Delaware law, and its substantial and continuing contacts with the State.

11. On information and belief, Teva Industries regularly transacts business within this District, including but not limited to directing the operations and management of Teva USA, as well as shipping pharmaceuticals to Teva USA from locations outside the United States for distribution by Teva USA within the United States generally, and within this District specifically.

12. On information and belief, Teva USA acts as an agent of Teva Industries with respect to the acts complained of herein.

13. On information and belief, the acts of Teva USA complained of herein were done at the direction of, with the authorization of, with the cooperation, participation, and assistance of, and, in part, for the benefit of Teva Industries.

14. On information and belief, Teva Industries directed Teva USA to perform the acts complained of herein to, in whole or in part, shield itself from liability for patent infringement based upon those acts.

15. Teva USA's acts and contacts with this District, as an agent of Teva Industries, are attributable to Teva Industries for jurisdictional purposes.

16. Teva Industries is subject to the personal jurisdiction in this District by virtue of, *inter alia,* its incorporation of Teva USA in Delaware, its conduct of business in this District, its purposeful availment of the rights and benefits of Delaware law, and its substantial and continuing contacts with the State.

17. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391(b), (c) and (d), and 1400(b).

FACTS PERTINENT TO ALL CLAIMS FOR RELIEF

18. On December 9, 1986, the United States Patent and Trademark Office ("the PTO") issued U.S. Patent No. 4,628,098 ("the '098 Patent"), entitled "2-[2-Pyridylmethylthio-(Sulfinyl)-]Benzimidazoles," to Takeda Chemical Industries, Ltd., the assignee of the named inventors Akira Nohara and Yoshitaka Maki. Plaintiff Takeda is the record owner of the '098 Patent, and Plaintiff TAP is the exclusive licensee. A copy of the '098 Patent is attached hereto as Exhibit A.

19. The original expiration date of the '098 Patent was July 29, 2005.

20. On January 6, 1997, the PTO granted the '098 Patent a term extension of 1381 days pursuant to 35 U.S.C. § 156, extending the expiration date of the '098 Patent to May 10, 2009.

21. On September 3, 1991, the PTO issued U.S. Patent No. 5,045,321 ("the '321 Patent"), entitled "Stabilized Pharmaceutical Composition and Its Production," to Takeda Chemical Industries, Ltd., the assignee of the named inventors Tadashi Makino, Tetsuro Tabata, and Shin-ichiro Hirai. Plaintiff Takeda is the record owner of the '321 Patent, and Plaintiff TAP is the exclusive licensee. A copy of the '321 Patent is attached hereto as Exhibit B.

22. On November 7, 1995, the PTO issued U.S. Patent No. 5,464,632, entitled "Rapidly Disintegratable Multiparticular Tablet," to Laboratoires Prographarm, the assignee of the named inventors Gerard Cousin, Etienne Bruna, and Edouard Gendrot. Laboratoires Prographarm granted Plaintiff Takeda an exclusive license to the '632 Patent with the right to sublicense. Plaintiff Ethypharm subsequently acquired Laboratoires Prographarm and is the record owner of the '632 Patent. Plaintiff TAP is the exclusive sublicensee to the '632 Patent. On February 20, 2001, the PTO issued a Reexamination Certificate for the '632 Patent. A copy of the '632 Patent and its Reexamination Certificate is attached hereto as Exhibit C.

23. On December 11, 2001, the PTO issued U.S. Patent No. 6,328,994 ("the '994 Patent"), entitled "Orally Disintegrating Tablets," to Takeda Chemical Industries, Ltd., the assignee of the named inventors Toshihiro Shimizu, Shuji Morimoto, and Tetsuro Tabata. Plaintiff Takeda is the record owner of the '994 Patent, and Plaintiff TAP is the exclusive licensee. A copy of the '994 Patent is attached hereto as Exhibit D.

24. On August 30, 2002, the United States Food and Drug Administration ("FDA") approved New Drug Application ("NDA") No. 21-428 for lansoprazole delayed release orally disintegrating tablets, 15 and 30 mg. TAP is the holder of NDA No. 21-428 for lansoprazole delayed release orally disintegrating tablets, which it sells under the name Prevacid® SoluTab™.

25. The '098, '321, '632 and '994 Patents (collectively, "the patents-in-suit") are listed in a publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations* (known as the "Orange Book") as covering Prevacid® SoluTab™, delayed release orally disintegrating tablets, 15 and 30 mg.

26. On information and belief, through the coordinated efforts of research and development staff in Israel, Europe and North America, Teva Industries seeks constantly to expand the range of generic products it sells.

27. On information and belief, Teva USA and Teva Industries collaborate in the manufacture, marketing and sale of many pharmaceutical products (including generic drug products manufactured and sold pursuant to an approved abbreviated new drug application) within the United States generally and the State of Delaware specifically.

28. On information and belief, Teva Industries actively reviews pharmaceutical patents and seeks opportunities to challenge those patents.

29. On information and belief, Teva Industries reviewed the patents-in-suit and certain commercial and economic information relating to Prevacid® SoluTab™, including estimates of the revenues generated by the sale of Prevacid® SoluTab™, and decided to file an Abbreviated New Drug Application ("ANDA"), seeking approval to market lansoprazole delayed release orally disintegrating tablets.

30. On information and belief, Teva USA and Teva Industries collaborated in the research, development, preparation and filing of Abbreviated New Drug Application ("ANDA") No. 78-730 for lansoprazole delayed release orally disintegrating tablets.

31. On information and belief, Teva USA submitted to FDA ANDA No. 78-730 seeking approval to engage in the commercial manufacture, use and sale of lansoprazole delayed release orally disintegrating tablets, 15 and 30 mg, prior to the expiration of the patents-in-suit.

32. Plaintiffs have received a letter dated April 12, 2007 from Teva USA notifying them that Teva USA's ANDA No. 78-730 includes a certification under 21 U.S.C.

§ 355(j)(2)(A)(vii)(IV) (a "Paragraph IV certification") that, in Teva USA's opinion, the patents-in-suit are invalid, unenforceable or will not be infringed by the commercial manufacture, use or sale of the lansoprazole delayed release orally disintegrating tablet products described in ANDA No. 78-730.

33. On information and belief, Teva Industries made the ultimate decision to file ANDA No. 78-730 with the FDA, and encouraged and directed Teva USA to file ANDA No. 78-730 and the Paragraph IV certification, and Teva USA did so at Teva Industries' direction.

34. On information and belief, Teva Industries was necessarily aware of the patents-in-suit when it directed Teva USA to file ANDA No. 78-730 and the Paragraph IV certification.

35. Plaintiffs commenced this action within 45 days of the date they received Teva USA's notice of ANDA No. 78-730 containing the Paragraph IV certification.

36. On information and belief, Teva USA and Teva Industries continue to collaborate in seeking approval of ANDA No. 78-730 from the FDA and intend to collaborate in the commercial manufacture, marketing, and sale of lansoprazole delayed release orally disintegrating tablets (including commercial marketing and sale of such products in the State of Delaware) in the event that FDA approves ANDA No. 78-730.

FIRST CLAIM FOR RELIEF
DIRECT INFRINGEMENT OF THE '098 PATENT BY TEVA USA AND TEVA INDUSTRIES

37. Plaintiffs Takeda and TAP repeat and reallege each and every allegation contained in paragraphs 1 through 36 hereof, as if fully set forth herein.

38. Through the conduct alleged above, Teva USA and Teva Industries (collectively "Teva") have directly infringed, and continue to directly infringe, one or more claims of the '098 Patent.

39. By filing ANDA No. 78-730 with a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of the lansoprazole delayed release orally disintegrating tablet products described therein, prior to the expiration of the '098 Patent, Teva has infringed the '098 Patent under 35 U.S.C. § 271(e)(2).

40. Teva was aware of the existence of the '098 Patent prior to filing ANDA No. 78-730, but took such action knowing that it would constitute an infringement of the '098 Patent.

41. On information and belief, Teva acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '098 Patent.

42. Teva does not dispute that the lansoprazole delayed release orally disintegrating tablet products described in ANDA No. 78-730 infringe claims 1, 2, 5, 6, 8, and 10 of the '098 Patent. Instead, Teva's Paragraph IV certification is premised upon a baseless assertion that claims 1, 2, 5, 6, 8, and 10 of the '098 Patent are invalid as obvious under 35 U.S.C. § 103 or unenforceable for inequitable conduct.

43. Teva disregarded its duty to exercise due care by making these baseless assertions of invalidity and unenforceability, and therefore, this case is "exceptional" as described in 35 U.S.C. § 285.

44. Plaintiffs Takeda and TAP will be irreparably harmed if Teva is not enjoined from infringing the '098 Patent.

SECOND CLAIM FOR RELIEF
INDUCEMENT OF INFRINGEMENT OF THE '098 PATENT BY TEVA INDUSTRIES

45. Plaintiffs Takeda and TAP repeat and reallege each and every allegation contained in paragraphs 1 through 44 hereof, as if fully set forth herein.

46. Through the conduct alleged above, Teva Industries has knowingly and actively induced Teva USA to infringe, and continue to infringe, one or more claims of the '098 Patent.

47. By reason of Teva Industries' inducement of Teva USA's direct infringement of the '098 Patent, Teva Industries has caused and continues to cause irreparable harm to Plaintiffs Takeda and TAP.

48. On information and belief, Teva Industries' inducement of Teva USA's direct infringement of the '098 Patent will continue unless enjoined by this Court.

49. Plaintiffs Takeda and TAP have no adequate remedy at law for Teva Industries' inducement of Teva USA's direct infringement of the '098 Patent.

50. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorneys' fees.

THIRD CLAIM FOR RELIEF
DIRECT INFRINGEMENT OF THE '321 PATENT BY TEVA USA AND TEVA INDUSTRIES

51. Plaintiffs Takeda and TAP repeat and reallege each and every allegation contained in paragraphs 1 through 50 hereof, as if fully set forth herein.

52. Through the conduct alleged above, Teva has directly infringed, and continues to directly infringe, one or more claims of the '321 Patent.

53. By filing ANDA No. 78-730 with a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of lansoprazole delayed

release orally disintegrating tablets, 15 and 30 mg, prior to the expiration of the '321 Patent, Teva has infringed the '321 Patent under 35 U.S.C. § 271(e)(2).

54. Teva was aware of the existence of the '321 Patent prior to filing ANDA No. 78-730, but took such action knowing that it would constitute an infringement of the '321 Patent.

55. On information and belief, Teva acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '321 Patent.

56. Teva's conduct renders this case "exceptional" as described in 35 U.S.C. § 285.

57. Plaintiffs Takeda and TAP will be irreparably harmed if Teva is not enjoined from infringing the '321 Patent.

FOURTH CLAIM FOR RELIEF
INDUCEMENT OF INFRINGEMENT OF THE '321 PATENT BY TEVA INDUSTRIES

58. Plaintiffs Takeda and TAP repeat and reallege each and every allegation contained in paragraphs 1 through 57 hereof, as if fully set forth herein.

59. Through the conduct alleged above, Teva Industries has knowingly and actively induced Teva USA to infringe, and continue to infringe, one or more claims of the '321 Patent.

60. By reason of Teva Industries' inducement of Teva USA's direct infringement of the '321 Patent, Teva Industries has caused and continues to cause irreparable harm to Plaintiffs Takeda and TAP.

61. On information and belief, Teva Industries' inducement of Teva USA's direct infringement of the '321 Patent will continue unless enjoined by this Court.

62. Plaintiffs Takeda and TAP have no adequate remedy at law for Teva Industries' inducement of Teva USA's direct infringement of the '321 Patent.

63. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorneys' fees.

FIFTH CLAIM FOR RELIEF
DIRECT INFRINGEMENT OF THE '632 PATENT BY TEVA USA AND TEVA INDUSTRIES

64. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 63 hereof, as if fully set forth herein.

65. Through the conduct alleged above, Teva has directly infringed, and continues to directly infringe, one or more claims of the '632 Patent.

66. By filing ANDA No. 78-730 with a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of lansoprazole delayed release orally disintegrating tablets, 15 and 30 mg, prior to the expiration of the '632 Patent, Teva has infringed the '632 Patent under 35 U.S.C. § 271(e)(2).

67. Teva was aware of the existence of the '632 Patent prior to filing ANDA No. 78-730, but took such action knowing that it would constitute an infringement of the '632 Patent.

68. On information and belief, Teva acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '632 Patent.

69. Teva's conduct renders this case "exceptional" as described in 35 U.S.C. § 285.

70. Plaintiffs will be irreparably harmed if Teva is not enjoined from infringing the '632 Patent.

SIXTH CLAIM FOR RELIEF
INDUCEMENT OF INFRINGEMENT OF THE '632 PATENT BY TEVA INDUSTRIES

71. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 70 hereof, as if fully set forth herein.

72. Through the conduct alleged above, Teva Industries has knowingly and actively induced Teva USA to infringe, and continue to infringe, one or more claims of the '632 Patent.

73. By reason of Teva Industries' inducement of Teva USA's direct infringement of the '632 Patent, Teva Industries has caused and continues to cause irreparable harm to Plaintiffs.

74. On information and belief, Teva Industries' inducement of Teva USA's direct infringement of the '632 Patent will continue unless enjoined by this Court.

75. Plaintiffs have no adequate remedy at law for Teva Industries' inducement of Teva USA's direct infringement of the '632 Patent.

76. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorneys' fees.

SEVENTH CLAIM FOR RELIEF
DIRECT INFRINGEMENT OF THE '994 PATENT BY TEVA USA AND TEVA INDUSTRIES

77. Plaintiffs Takeda and TAP repeat and reallege each and every allegation contained in paragraphs 1 through 76 hereof, as if fully set forth herein.

78. Through the conduct alleged above, Teva has directly infringed, and continues to directly infringe, one or more claims of the '994 Patent.

79. By filing ANDA No. 78-730 with a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of lansoprazole delayed

release orally disintegrating tablets, 15 and 30 mg, prior to the expiration of the '994 Patent, Teva has infringed the '994 Patent under 35 U.S.C. § 271(e)(2).

80. Teva was aware of the existence of the '994 Patent prior to filing ANDA No. 78-730, but took such action knowing that it would constitute an infringement of the '994 Patent.

81. On information and belief, Teva acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '994 Patent.

82. Teva's conduct renders this case "exceptional" as described in 35 U.S.C. § 285.

83. Plaintiffs Takeda and TAP will be irreparably harmed if Teva is not enjoined from infringing the '994 Patent.

EIGHTH CLAIM FOR RELIEF
INDUCEMENT OF INFRINGEMENT OF THE '994 PATENT BY TEVA INDUSTRIES

84. Plaintiffs Takeda and TAP repeat and reallege each and every allegation contained in paragraphs 1 through 83 hereof, as if fully set forth herein.

85. Through the conduct alleged above, Teva Industries has knowingly and actively induced Teva USA to infringe, and continue to infringe, one or more claims of the '994 Patent.

86. By reason of Teva Industries' inducement of Teva USA's direct infringement of the '994 Patent, Teva Industries has caused and continues to cause irreparable harm to Plaintiffs Takeda and TAP.

87. On information and belief, Teva Industries' inducement of Teva USA's direct infringement of the '994 Patent will continue unless enjoined by this Court.

88. Plaintiffs Takeda and TAP have no adequate remedy at law for Teva Industries' inducement of Teva USA's direct infringement of the '994 Patent.

89. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorneys' fees.

WHEREFORE, Plaintiffs respectfully request the following relief:

A. An order adjudging and decreeing that Teva USA and Teva Industries have infringed the patents-in-suit;

B. An order adjudging and decreeing that Teva Industries has induced infringement of the patents-in-suit;

C. An order pursuant to 35 U.S.C. § 271(e)(4)(A) decreeing that the effective date of any approval of ANDA No. 78-730 be no earlier than the expiration date of the last of the patents-in-suit, including any extensions;

D. A preliminary and permanent injunction pursuant to 35 U.S.C. § 271(e)(4)(B) restraining and enjoining Teva USA and Teva Industries, their officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the lansoprazole products described in ANDA No. 78-730 or any other ANDA not colorably different from ANDA No. 78-730 until the expiration date of the last of the patents-in-suit, including any extensions;

E. A declaration that this case is exceptional and an award of attorneys' fees under 35 U.S.C. § 285 and costs and expenses in this action; and

F. Such other and further relief as the Court may deem just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Mary B. Graham

Jack B. Blumenfeld (#1014)
Mary B. Graham (#2256)
Rodger D. Smith II (#3778)
James W. Parrett, Jr. (#4292)
1201 N. Market Street
P.O. Box 1347
Wilmington, DE 19801
302.658.9200

Attorneys for Takeda Pharmaceutical Company Limited, TAP Pharmaceutical Products Inc. and Ethypharm, S.A.

OF COUNSEL:

Eric J. Lobenfeld
Tedd W. Van Buskirk
Arlene L. Chow
Dillon Kim
HOGAN & HARTSON LLP
875 Third Avenue
New York, New York 10022
212.918.3000

Philippe Y. Riesen
HOGAN & HARTSON LLP
Shinjuku Center Building, 46th Floor
25-1 Nishi-Shinjuku 1-chome
Shinjuku, Tokyo 163-0646
Japan
(81) 3-5908-4070

Richard de Bodo
HOGAN & HARTSON LLP
1999 Avenue of the Stars, Suite 1400
Los Angeles, CA 90067
310.785.4600

Attorneys for Takeda Pharmaceutical Company Limited and Ethypharm, S.A.

William F. Cavanaugh
Stuart E. Pollack
Chad J. Peterman
PATTERSON BELKNAP WEBB & TYLER LLP
1133 Avenue of the Americas
New York, New York 10036
212.336.2000

Attorneys for TAP Pharmaceutical Products Inc.

Dated: May 25, 2007
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